Impact of hyponatremia correction on the risk for 30-day readmission and death in patients with congestive heart failure

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Abstract: OBJECTIVE: The study objective was to compare the 30-day readmission rate and mortality between patients with heart failure who have persistent hyponatremia during hospitalization and patients who have their admission hyponatremia corrected before discharge. METHODS: This large retrospective cohort study included all adult patients admitted with a diagnosis of congestive heart failure to a tertiary-care hospital between July 2003 and October 2009. We compared the readmission rate and mortality 30 days after discharge between patients with persistent hyponatremia (ie, low sodium level at both admission and discharge) and patients with hyponatremia correction during hospitalization. RESULTS: Among the 4295 eligible patients with hyponatremia at admission, 1799 (41.9%) did not have their sodium level corrected at discharge. Overall, 1269 patients (29.5%) had a 30-day unplanned readmission or died. In a multivariable logistic regression analysis, the absence of hyponatremia correction was associated with a 45% increase in the odds of having a 30-day unplanned readmission or death (odds ratio, 1.45; 95% confidence interval, 1.27-1.67). Among patients with persistent hyponatremia, those with more severe hyponatremia at discharge (<130 mm/L) had a higher odds (odds ratio, 1.68; 95% confidence interval, 1.32-2.14) of having a 30-day readmission or death than those with less severe hyponatremia at discharge (130-134 mm/L). CONCLUSIONS: The absence of correction of hyponatremia over the course of hospitalization was frequent and independently associated with an increase of approximately 50% in the odds of having a 30-day unplanned readmission or death. This association appeared to be independent of heart failure severity.

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Impact of Hyponatremia Correction on the Risk for 30-Day Readmission and Death in Patients with Congestive Heart Failure

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Objectives: To compare the 30-day readmission rate and mortality between heart failure patients who have persistent hyponatremia during hospitalization and those who have their admission hyponatremia corrected before discharge.

Methods: This large retrospective cohort study included all adult patients admitted with a diagnosis of congestive heart failure to a tertiary-care hospital between July 2003 and October 2009. We compared the readmission rate and mortality 30-day after discharge between patients with persistent hyponatremia (i.e. low sodium level at both admission and discharge) and patients with hyponatremia correction during hospitalization.

Results: Among the 4,295 eligible patients with hyponatremia at admission, 1,799 (41.9%) did not have their sodium level corrected at discharge. Overall, 1,269 (29.5%) patients had a 30-day unplanned readmission or died. In a multivariable logistic regression analysis, the absence of hyponatremia correction was associated with a 45% increase in the odds of having a 30-day unplanned readmission or death (odds ratio 1.45; 95%CI [1.27-1.67]). Among patients with persistent hyponatremia, those with more severe hyponatremia at discharge (<130 mm/L) had a higher odds (odds ratio 1.68; 95%CI [1.32-2.14]) of having a 30-day readmission or death, than those with less severe hyponatremia at discharge (130-134 mm/L).

Conclusions: The absence of correction of hyponatremia over the course of hospitalization was frequent and independently associated with an increase of nearly 50% in the odds of having a 30-day unplanned readmission or death. This association appeared to be independent from heart failure severity.

Introduction

Hyponatremia is present at admission in about 20-30% of the patients hospitalized for heart failure,[1-4] and is associated with an increased risk for readmission and death in congestive heart failure patients compared to congestive heart failure patients without hyponatremia at admission.[5-10] However, the prognostic impact of persistent hyponatremia throughout the hospitalization has not been explored to the same extent.[11, 12]

One study found that the change in sodium level after hospital discharge was a strong predictor of long-term survival in patients with heart failure,[13] however, little is known in terms of the impact of sodium changes during the hospitalization. Two small post-hoc analyses of randomized control trials found conflicting results in terms of mortality risk and may not truly represent the general heart failure population.[14, 15]

Our hypothesis was that heart failure patients with persistent hyponatremia would be at higher risk for worse post-discharge outcomes than those with corrected sodium levels. Therefore, we compared the 30-day readmission rate and mortality after discharge between patients with persistent hyponatremia and patients with hyponatremia correction during hospitalization.

Materials and Methods

Design and Setting

The study was designed as a retrospective cohort study and was conducted at Brigham and Women's Hospital, Boston, Massachusetts, which is a large tertiary referral center and teaching hospital with approximately 750 beds. The study was approved by the institutional review board, and patient consent was waived. Our study followed strengthening of reporting observational studies in epidemiology (STROBE) guidelines.[16]

Population

All adult (age ≥18) inpatients with congestive heart failure, admitted after 6/30/2003 and discharged before 11/1/2009, were identified. Diagnosis of congestive heart failure was identified by International Classification of Diseases [ICD], World Health Organization, Geneva, Switzerland, version 9: 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.0-428.9. All types of heart failure were included, without differentiating the heart failure with preserved and reduced ejection fraction. Only patients with a hyponatremia at admission were included, defined as a sodium level of less than 135 mmol/L at admission. Patients were excluded if they stayed ≤24 hours at the hospital, died during the hospitalization, were transferred to another hospital or care center, or left the hospital against medical advice.

Outcome

The primary outcome was any non-elective hospital readmission or all-cause death within 30 days after hospital discharge. Readmissions to the same hospital network were captured using the electronic health record. We used the Social Security Death Index to identify the patients who died within 30 days after the discharge date. Secondary outcomes included each single component of the primary outcome separately, as well as any 30-day unplanned readmission due to congestive heart failure.

Exposure

The exposure of interest was the correction of hyponatremia during the hospital course, and was grouped into two categories: (i) hyponatremia was persistent over the hospital stay, defined as a sodium level <135 mmol/L at both admission and discharge, and (ii) the hyponatremia was corrected during the hospitalization, defined as a sodium level <135 mmol/L at admission, but ≥135 mmol/L at discharge.

Co-variables

Potential confounders were selected based on a priori knowledge and according to the medical literature,[17-20] and included: age, gender, race, number of admissions within the last 6 months prior to the index admission, unplanned index admission versus elective, length of stay, atrial flutter or atrial fibrillation (ICD-9 codes 427.31-427.32), ischemic heart disease (ICD-9 codes 410.00-414.9), cancer (ICD-9 codes 140.0-239.9), chronic obstructive pulmonary disease (ICD-9 codes 491.0-492.8, 493.20-493.22 and 496), diabetes (ICD-9 codes 249.00-250.93), and chronic kidney disease (ICD-9 codes 585.1-586). The severity of congestive heart failure was assessed using the last available laboratory value of the Brain Natriuretic Peptide (BNP) and/or the last measurement of the ejection fraction (EF) prior to discharge.

Statistical Analysis

Baseline characteristics were presented as numbers and percentages for categorical variables, means including standard deviations (SD) or medians with interquartile ranges (IQR) for continuous variables. The proportions of missing values were separately grouped if more than 1% were missing.

The unit of analysis was the index hospitalization. Multivariable logistic regression analyses were performed to calculate adjusted odds ratios (OR) and 95% confidence intervals (95% CI). All models were adjusted for the potential confounders mentioned above.

In a subset of patients with available BNP levels or EF values, we additionally adjusted for the severity of congestive heart failure. If the last BNP was 360 pg/mL or greater,[21] the heart failure was categorized as severe. In cases without any BNP measurements but with available ejection fraction, the congestive heart failure was categorized as severe if the last ejection fraction was 40% or less.[22]

All tests were conducted as two-sided at a 0.05 level of significance. Calculations and analyses were performed using the software R, version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Among the 38,792 inpatients discharged with a diagnosis of congestive heart failure, 6,602 (17.0%) had a sodium level <135 mmol/L at admission (Fig. 1). A total of 4,295 hospitalizations were eligible for further investigation. Among those patients, 1,799 patients (41.9%) had a persistent hyponatremia throughout the hospital stay. The mean sodium levels at admission and discharge for the entire cohort were 131.2 (SD 3.3) and 135.0 (SD 4.0) mmol/L, respectively. The baseline characteristics of the cohort are presented in Table 1. The patients with persistent hyponatremia had a sodium level 1.7 mmol/L lower at admission and 6.4 mmol/L lower at discharge in comparison to the patients who had their hyponatremia corrected during the index hospital stay. The median length of the index hospitalization was 6 days in both groups with and without persistent hyponatremia.

30-Day Unplanned Readmission or Death

Among the eligible patients, 1,269 (29.5%) were readmitted or died within 30 days after their discharge from the index hospitalization. The proportion of patients who had the composite endpoint and had a persistent hyponatremia during the index hospitalization was 33.7% (n=606; Table 2). The crude odds ratio (OR) for having a 30-day unplanned readmission or death was 1.40 (95% CI [1.23 to 1.60]). In a multivariable logistic regression, the persistent hyponatremia was associated with a statistically significant 45% increase in the odds of readmission or death within 30 days after discharge (adjusted OR 1.45; 95% CI [1.27 to 1.67]; Table 3). Further factors statistically significantly associated with the primary outcome of interest were the race ‘black’, higher number of previous admissions, unplanned hospitalization (vs. elective), longer length of stay, lack of ischemic heart disease, and presence of cancer. We found no effect modification for all baseline

characteristics, except for length of stay (p-value for interaction = 0.01; Fig. 2): the effect of persistent hyponatremia on the risk of 30-day readmission or death appeared higher with increasing length of stay.

Among patients with persistent hyponatremia, those with more severe hyponatremia at discharge (<130 mm/L) had a higher odds (adjusted OR 1.68; 95%CI [1.32-2.14]) of having a 30-day readmission or death, than those with less severe hyponatremia at discharge (130-134 mm/L).

Specific 30-Day Unplanned Readmission

Within 30 days after discharge, 1,080 (25.1%) patients were unexpectedly readmitted. In a multivariable logistic regression model, persistent hyponatremia was associated with a specific 30-day unplanned readmission (adjusted OR 1.28; 95% CI [1.11 to 1.48]). Further factors associated with this secondary outcome were female gender (adjusted OR 1.18; 95%CI [1.02 to 1.37]), the race “black” (adjusted OR 1.34; 95%CI [1.08 to 1.66], race ”hispanic” (adjusted OR 1.37; 95% CI [1.03 to 1.80]), more previous admissions in the last 6 months (adjusted OR 1.29; 95%CI [1.23 to 1.35]), unplanned hospitalization (vs. elective) (adjusted OR 1.78; 95%CI [1.37 to 2.34]), and presence of cancer (adjusted OR 1.49; 95%CI [1.24 to 1.78]).

Among the main diagnoses of 30-day unplanned readmissions, 21.4% (106/495) of patients with persistent hyponatremia were readmitted with a main diagnosis of heart failure vs. 17.1% (100/585) of patients with corrected hyponatremia at index discharge. This difference was however not statistically significant in a multivariable logistic regression (adjusted OR 1.30; 95% CI [0.94 to 1.79]).

Death within 30 Days after Discharge

Overall, 296 (6.9%) patients died within 30 days after discharge. The multivariable logistic regression model revealed that the exposure of persistent hyponatremia was significantly associated with a nearly 2-fold increase in the odds of death within 30 days after discharge (adjusted OR 1.99; 95% CI [1.56 to 2.55]). Also

statistically significantly associated with this outcome were in this model: age (adjusted OR 1.02; 95% CI [1.01 to 1.03]), more frequent previous admissions in the last 6 months (adjusted OR 1.14; 95% CI [1.06 to 1.22]), unplanned hospitalization (vs. elective) (adjusted OR 1.80; 95% CI [1.14 to 3.03]), longer length of stay (adjusted OR 1.02; 95% CI [1.01 to 1.03]), diagnosis of ischemic heart disease (adjusted OR 0.71; 95% CI [0.54 to 0.93]), diagnosis of cancer (adjusted OR 3.37; 95% CI [2.58 to 4.39]), diagnosis of atrial fibrillation (adjusted OR 1.35; 95% CI [1.04 to 1.76]), and diagnosis of COPD (adjusted OR 1.37; 95% CI [1.01 to 1.84]).

Severity of congestive heart failure

To exclude confounding by heart failure severity, we created a subcohort that included the 1,544 patients with either a BNP of 360 pg/mL or greater (n=1,357) or a recent EF measurement of less than 40% (n=187). In this subcohort, a total of 906 (58.7%) patients were identified with severe heart failure, and a total of 471 (30.5%) were unexpectedly readmitted or died within 30 days after discharge. In a multivariable logistic regression, persistent hyponatremia was still statistically significantly associated with a higher risk for unplanned readmission or death within 30 days after discharge (OR 1.32; 95% CI [1.05 to 1.66]) after additional adjustment for heart failure severity. The covariate 'severe heart failure' revealed a statistically non-significant odds ratio of 1.17 (95% CI [0.93 to 1.49]).

Hyponatremia at readmission

Among the unplanned readmissions, the most frequent main diagnosis was again congestive heart failure or acute lung edema in 206 cases (19.1%).

Nine patients (0.8%) were readmitted due to hypo-osmolality and/or hyponatremia based on the main ICD-9 diagnosis. However, we found that overall, 53.3% (n=576) of the patients had again hyponatremia at time of

readmission. Among those who had a persistent hyponatremia during the index hospitalization and were readmitted within 30 days, 71.7% (n=355) presented again with hyponatremia at time of readmission. In comparison, in the group with corrected hyponatremia during the index hospitalization, only 37.8% (n=221) presented again with hyponatremia at time of readmission.

Discussion

In this heart failure population with hyponatremia at admission, we found that 42% of the patients had persistent hyponatremia over the course of hospitalization. Persistent hyponatremia was associated with an increase of nearly 50% in the odds of having a 30-day unplanned readmission or death, and this association appeared to be independent of heart failure severity.

Hyponatremia and the risk of readmission or death in heart failure patients

Several relatively small studies have shown that hyponatremia is associated with readmission and death in heart failure patients.[23] However, little is known about the impact of persistent hyponatremia, in comparison to patients who have their hyponatremia corrected during the hospital stay. If these patients with persistent hyponatremia have a specific risk profile is unknown. In a post-hoc analysis of a randomized controlled trial in selected patients with severe heart failure (EF<30%), persistent hyponatremia in 71 patients was associated with readmission and death at 6 months.[11] However, in this study, persistent hyponatremia was compared only to patients with a normal sodium level at admission. Similarly, the EVEREST study found an increased mortality in patients with hyponatremia, also only in comparison with normonatremic patients.[24] In two other post-hoc analyses of randomized controlled trials comparing tolvaptan and milrinone to placebo, the impact of hyponatremia correction on 60-day mortality was conflicting.[14, 15] Rossi et al. found in the ACTIV trial a reduced 60-day mortality in patients who improved their sodium of 2 mmol/L or more between admission and the last sodium level available in an every other week post-hospital discharge follow-up.[14] Klein et al. in the OPTIM-CHF study did not find a significant different mortality among 244 patients who had an admission sodium level in the lowest quartile.[15] It is however to notice that this lowest quartile had a only a moderate low sodium level with a median of 134 mmol/L (IQR 132-135). Moreover, these small post-hoc analyses from selected patients of randomized control studies focused mainly on mortality and were restricted to patients

with severe heart failure, and cannot be therefore generalized to the "real world" population of hospitalized patients with heart failure.

Possible explanations for the association between persistent hyponatremia and the risk for 30-day unplanned readmission and death may include: 1) persistent hyponatremia reflects a heart failure more difficult to control, and therefore these patients have an increased risk for readmission, mainly heart failure-related. This independent association might be related to elevated levels of plasma renin as previously hypothesized.[23] In our cohort, however, we did not find a statistically significant association between persistent hyponatremia and readmission due to heart failure that would support this hypothesis; 2) persistent hyponatremia is a marker of comorbidities, which in turn increase the risk for readmissions.

Study limitations

This study has several limitations. First, it is a single center study, and results might not be generalizable to other sites. However, as opposed to the previous studies, we included general heart failure patients, and not only severe heart failure patients, improving the generalizability of our findings. Second, measurements of heart failure severity were only available in a subset of patients. However, whether or not confounding is responsible for this association is unclear, since previous data have shown that sodium levels do not differ significantly according to the EF [25], which seems to be corroborated by the absence of change the association in our subanalysis. Third, we didn't assess sodium level changes between admission and discharge. Some patients may have had their hyponatremia corrected before it recurred. Fourth, we didn't assess the medical therapy during the hospital stay. We cannot therefore completely exclude that a lack of adequate medical therapy is partly responsible for the persistence of hyponatremia in some patients. Finally, the association may or may not be causal, and we could not assess causality in this study. Therefore it remains unknown whether correction of the hyponatremia before discharge would reduce the risk for readmission and death.

While a potential effect of hyponatremia correction in heart failure patients warrants further investigation, patients who have their hyponatremia not corrected before hospital discharge may benefit from closer follow-up.

Conclusions

In a large population of heart failure patients, persistent hyponatremia until discharge increased the risk for 30-day unplanned readmission and death in comparison with patients who had their sodium levels increased to normal values at hospital discharge. This association appeared to be independent from heart failure severity. Additional studies could explore whether or not more aggressive correction of hyponatremia is beneficial in this population.

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Author contributions

JDD designed the study, wrote the study protocol, developed the analytic plan, and contributed to the statistical analyses. PEB managed the data and performed the statistical analyses. JDD and PEB drafted the manuscript. All authors were involved in the interpretation of the data, as well as the editing and final approval of the manuscript. All authors had full access to the data. JDD is the guarantor.

Conflicts of interest: none.

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Figure 1. Study flowchart.

Figure 2. Subgroup analysis for risk of 30-day unplanned readmission or death with persistent hyponatremia

*chronic obstructive pulmonary disease.

Footnote: only length of stay showed a statistically significant p-value for interaction (p=0.014).

Table 1. Baseline characteristics

Variable	Overall (n=4,295)		Persistent Hyponatremia (n=1,799)		Sodium level normalized (n=2,496)	
Age [years], mean (SD)	67.0	(15.6)	67.1	(15.9)	66.9	(15.4)
Gender, n (%)						
Male	2218	(51.6)	913	(50.8)	1305	(52.3)
Female	2077	(48.4)	886	(49.2)	1191	(47.7)
Race, n (%)						
White	3271	(76.2)	1427	(79.3)	1844	(73.9)
Black	531	(12.4)	172	(9.6)	359	(14.4)
Hispanic	280	(6.5)	110	(6.1)	170	(6.8)
Other/Unknown	213	(5.0)	90	(5.0)	123	(4.9)
Marital status , n (%)						
Married/Partnered	2050	(47.7)	884	(49.1)	1166	(46.7)
Widowed/Divorced/ Separated	1196	(27.8)	511	(28.4)	685	(27.4)
Single	810	(18.9)	307	(17.1)	503	(20.2)
Other/Unknown	239	(5.6)	97	(5.4)	142	(5.7)
Insurance, n (%)						
Medicare	2342	(54.5)	993	(55.2)	1349	(54.0)
Commercial	1442	(33.6)	609	(33.9)	833	(33.4)
Free Care/Self Pay/ Other	261	(6.1)	106	(5.9)	155	(6.2)
Medicaid	250	(5.8)	91	(5.1)	159	(6.4)
Unplanned index admission, n (%)	3829	(89.2)	1570	(87.3)	2259	(90.5)

Length of stay of index admission [days], median (IQR)	6	(3-10)	6	(3-9)	6	(3-10)
Number of admissions during last 6 months, median (IQR)	0	(0-2)	1	(0-2)	0	(0-2)
Diabetes, n (%)	1392	(32.4)	531	(29.5)	861	(34.5)
Atrial flutter/fibrillation, n (%)	1463	(34.1)	644	(35.8)	819	(32.8)
Ischemic heart disease, n (%)	1909	(44.4)	759	(42.2)	1150	(46.1)
Cancer, n (%)	843	(19.6)	375	(20.8)	468	(18.8)
Chronic obstructive pulmonary disease, n (%)	759	(17.7)	300	(16.7)	459	(18.4)
Chronic kidney disease, n (%)	802	(18.7)	318	(17.7)	484	(19.4)
First sodium level [mmol/L], mean (SD)	131.2	(3.3)	130.2	(3.8)	131.9	(2.7)
Sodium change [mmol/L], mean (SD)	3.78	(4.27)	1.04	(3.77)	5.76	(3.44)
Last sodium level [mmol/L], mean (SD)	135.0	(4.0)	131.3	(2.7)	137.7	(2.2)

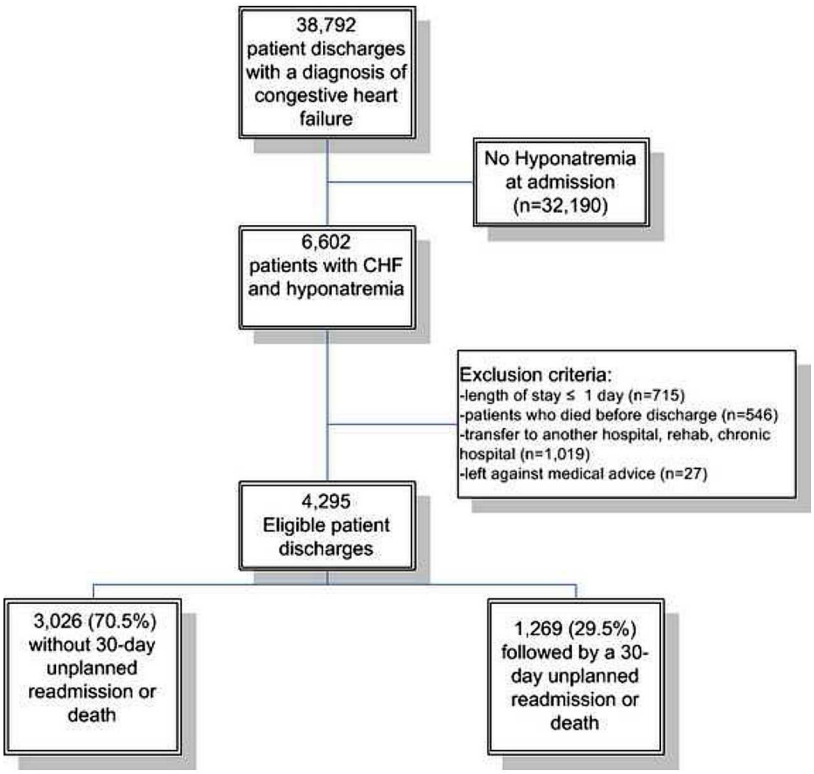
Table 2: Comparison of 30-day primary and secondary outcomes for persistent and corrected hyponatremia

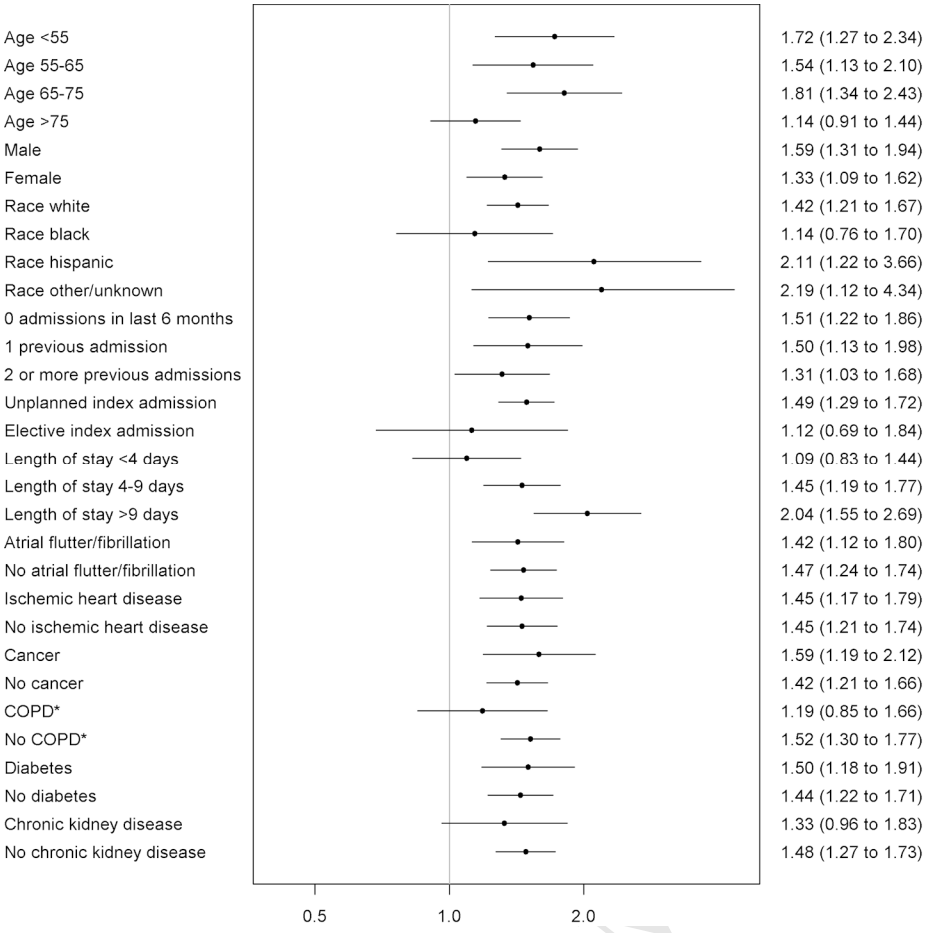
	30-day unplanned readmission or death	30-day unplanned readmission	Death
Persistent hyponatremia (N=1,799)	606 (33.7%)	495 (27.5%)	170 (9.4%)
Corrected hyponatremia (N=2,496)	663 (26.6%)	585 (23.4%)	126 (5.0%)
Adjusted OR (95% CI)	1.45 (1.27-1.67)	1.28 (1.11-1.48)	1.99 (1.56-2.55)

Table 3. Multivariable logistic regression for 30-day unplanned readmission or death.

Variable	Odds ratio	95% confidence interval
Persistent hyponatremia	1.45	1.27 to 1.67
Age, per additional year	1.00	1.00 to 1.01
Female vs. male	1.12	0.98 to 1.29
Race		
White	ref	
Black	1.31	1.06 to 1.61
Hispanic	1.31	1.00 to 1.72
Other/unknown	0.94	0.67 to 1.30
Number of admissions in the last 6 months, per additional admission	1.30	1.25 to 1.36
Unplanned vs. elective index admission	1.85	1.45 to 2.40
Length of stay, per additional day	1.01	1.00 to 1.01
Atrial flutter/fibrillation	1.07	0.92 to 1.24
Ischemic heart disease	0.85	0.74 to 0.99
Cancer	1.86	1.57 to 2.21
COPD*	1.01	0.84 to 1.21
Diabetes	1.12	0.97 to 1.31
Chronic kidney disease	1.03	0.86 to 1.23

* Chronic obstructive pulmonary disease





Clinical significance

- The prognostic impact of persistent hyponatremia in comparison to corrected hyponatremia before hospital discharge is unknown
- In a large study including heart failure patients who are admitted with hyponatremia, those who do not have their hyponatremia corrected before discharge have an increased risk of 50% for a 30-day unplanned readmission or death, and a two-fold increase risk for mortality, in comparison to those who have their hyponatremia corrected before discharge.
- Persistent hyponatremia at discharge may be a useful marker for post-discharge complications among heart failure patients, and those patients may benefit from closer follow-up.